Topics in Primary Care Medicine

Pharmacotherapy of Asthma

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Despite major recent therapeutic advances, asthma continues to be an important cause of morbidity and mortality worldwide. This persistent morbidity, despite the availability and widespread use of potent drugs that relax airway smooth muscle, has made it clear that airway smooth muscle contraction is only one component of the pathophysiology of asthma and does not by itself explain the clinical course of this disease. Both airway inflammation and mucus hypersecretion are prominent histologic features in patients dying of asthma, and both clinical and experimental evidence suggests that these factors play a major role in the clinical course of this disease. Although effective and reasonably well tolerated drugs are available to treat airway smooth muscle contraction, the current therapies for airway inflammation and mucus hypersecretion are much less satisfactory.

Bronchoconstriction

β-Adrenergic agonists are the most effective class of drugs presently available to inhibit contraction of airway smooth muscle. When administered by inhalation, even nonselective β-agonists such as isoproterenol cause potent relaxation of contracted airway smooth muscle in doses low enough to be free of significant systemic effects. Although a number of β_2-adrenergic agonists have been developed with relative selectivity for the β_2-adrenergic receptors present on airway smooth muscle, all of these drugs cause significant stimulation of β_1-receptors when they are given systemically in the doses required to relax airway smooth muscle. Furthermore, by causing relaxation of peripheral blood vessels (an effect of β_2-receptor stimulation) all of these agents can indirectly cause reflex tachycardia. Thus, the route of administration of a β-adrenergic agonist is a more important determinant of selective activation of pulmonary β-adrenergic receptors than is the pharmacologic specificity of the drug for β_2-receptors. Administration of these drugs by inhalation maximizes the desired effect—bronchodilation—and minimizes adverse effects. In contrast, oral, subcutaneous or intravenous administration of these drugs maximizes the potential for adverse effects for a given amount of bronchodilation. In theory, severe bronchoconstriction could prevent adequate delivery of inhaled drugs to contracted airway smooth muscle, limiting the efficacy of inhaled β-agonists. In practice, however, administration of small doses of these drugs by inhalation has been repeatedly shown to be either more effective than or as effective as the systemic administration of considerably larger doses. Furthermore, in patients treated with adequate doses of an inhaled β-agonist, an additional systemically administered β-agonist causes little or no additional bronchodilation, even in patients with the most severe airway obstruction. Thus, there is little rationale for routine administration of β-adrenergic agonists by any method other than inhalation.

The optimal dose of each inhaled β-adrenergic agonist has not been determined and probably varies considerably among patients. For instance, in some patients with mild asthma, two inhalations of metaproterenol sulfate from a metered-dose inhaler have been shown to produce maximal bronchodilation, whereas in patients with more severe asthma a significant dose-response has been shown to occur with up to eight inhalations of the same drug. Prevention of *induced* bronchoconstriction, a primary goal of the outpatient management of asthma, may require considerably larger doses than those required to maximize baseline bronchodilation. Thus the dose and frequency of administration of these drugs must be tailored to each patient. Optimal therapy commonly requires higher doses and shorter dosing intervals than those recommended by the drug manufacturer. Thus some patients require as many as four or five inhalations of metaproterenol as often as every two to four hours. When patients know that certain activities (such as exercise or sexual intercourse) predictably trigger bronchoconstriction, it is reasonable to add a supplemental dose of an inhaled β-agonist 15 minutes before they begin. The patient should be encouraged to titrate the dose of

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β-agonist upward (to a maximum of eight inhalations) until bronchoconstriction is reliably prevented or side effects occur. Although these high doses of inhaled β-adrenergic agonist frequently cause tremor or tachycardia, it is worth remembering that eight inhalations of metraproterenol, for example, deliver only one quarter of the dose contained in a single metaproterenol pill. Doses of inhaled β-agonists below five puffs rarely cause side effects.

Inhaled drugs can be administered by several different methods, including the metered-dose inhaler, the air-compressor nebulizer and intermittent positive pressure breathing (IPPB). The metered-dose inhaler is generally the preferred method because it is efficient, convenient, portable and minimizes dosing errors. When this device is used correctly, the resultant bronchodilation is at least equivalent to that achieved with the other methods. The major limitation to the use of the metered-dose inhaler is that patients frequently have difficulty mastering the correct technique. The patient should be instructed to hold the inhaler two inches in front of the mouth, to exhale first and then to activate the inhaler once while inhaling slowly. A ten-second breath-hold increases retention of the inhaled aerosol by increasing gravitational sedimentation. The inhaler should not be activated more than once during a breath. In fact, two puffs of a β-adrenergic agonist inhaled ten minutes apart have been shown to produce more bronchodilation than two puffs inhaled on successive breaths. Although with repeated coaching most patients can learn adequate (even if not perfect) technique, some cannot. In these patients, the use of available spacers can generally compensate for inadequate technique and allow effective use of a metered-dose inhaler. IPPB has no advantages over the air-compressor nebulizer and may rarely cause serious morbidity. It should thus not be used to administer bronchodilator drugs.

Theophylline and its metabolic precursors make up the other commonly used class of drugs thought to relax airway smooth muscle. In safe doses, these drugs are not as effective as β-adrenergic agonists either in reversing bronchoconstriction or in preventing induced bronchoconstriction. Like systemically administered β-adrenergic agonists, theophylline does not add significantly to the bronchodilation achieved by adequate doses of an inhaled β-agonist even in the emergency treatment of patients with severe airway obstruction. Theophylline does cause considerable toxic effects and occasional deaths when it accumulates in the blood stream in a high concentration. The principal toxic effects of theophylline are nausea, vomiting, tachycardia, anxiety and intractable seizures. It is thus difficult to justify the routine use of theophylline-containing drugs in the emergency treatment of acute bronchoconstriction. Recently, several studies have shown a potential beneficial effect of theophylline unrelated to bronchodilation—improvement in diaphragmatic contractility. If this effect is shown to be clinically important it may provide a rationale for the use of these drugs in selected patients with respiratory failure.

Although theophylline in commonly used doses is not as potent a bronchodilator as presently available β-adrenergic agonists, theophylline-containing drugs still have a role in the long-term management of asthma because of their long duration of action. Thus, whereas the longest acting β-adrenergic agonists presently available maintain maximal bronchodilation for only two to six hours, long-acting theophylline preparations can maintain maximal bronchodilation for 12 hours or longer. These drugs can therefore improve symptomatic control of asthma in patients who would otherwise require frequent high-dose administration of an inhaled β-adrenergic agonist. For similar reasons, long-acting theophylline preparations can be especially useful in patients with frequent nocturnal symptoms, or in patients with mild asthma who prefer the convenience of twice-a-day drug administration.

Whenever theophylline-containing drugs are prescribed the serum theophylline concentration should be periodically monitored to avoid inadvertent overdosing, since the pharmacokinetics of these drugs are notoriously variable both among patients and within any given patient. The simultaneous administration of numerous drugs, including cimetidine, allopurinol, erythromycin and propranolol hydrochloride, can significantly impair theophylline clearance and thus increase serum theophylline concentrations. Heart failure and hepatic dysfunction also impair theophylline clearance, sometimes greatly. Thus, if these drugs are administered to acutely ill patients who are in hospital and frequently receive other drugs, and who may have rapidly changing hepatic or cardiac function (or both), frequent monitoring of the serum theophylline concentration is mandatory.

When theophylline is administered to stable outpatients, it is reasonable to begin with a low dose (for example, 200 mg of a long-acting preparation such as Theo-Dur [anhydrous theophylline] every 12 hours for an otherwise healthy average-sized adult). The dose can then be adjusted upward if the patient's asthma is not adequately controlled and the theophylline blood concentration is less than 15 μg per ml. To avoid toxicity, an intravenous loading dose should not be given to patients who have been taking oral theophylline preparations and the initial maintenance dose for intravenous infusion should not exceed 0.5 mg per kg of body weight per hour. This dose should be cut in half in patients with liver disease or heart failure.

In patients with mild asthma, especially those with a predictable exogenous trigger for attacks such as allergens or exercise, therapy with cromolyn sulfate (one or two 20-mg capsules administered by inhalation four times a day or two capsules 15 minutes before exercise) can provide effective prophylaxis. However, inhaled β-adrenergic agonists are generally as effective as cromolyn in preventing exercise-induced bronchoconstriction and are considerably less expensive. In some patients the addition of cromolyn can reduce the dose of inhaled β-adrenergic agonist required to inhibit exercise-induced bronchoconstriction and can thus decrease the likelihood of side effects.

Although several other classes of drugs including calcium antagonists, α-adrenergic antagonists and muscarinic antagonists have been shown to reverse or inhibit bronchoconstriction, none of these drugs offers sufficient advantages over β-adrenergic agonists to justify their routine use in the treatment of asthma.

Airway Inflammation

The mechanisms underlying airway inflammation and edema in asthma are poorly understood. Consequently, there is little scientific basis for present approaches to treatment. Although the mechanism of the beneficial effect of corticosteroids on asthma is likewise poorly understood, these drugs are

thought to treat airway inflammation. This hypothesis fits well with the clinical observation that treatment with corticosteroids usually improves airway function in patients with status asthmaticus who do not improve after treatment with bronchodilators. The beneficial effects of corticosteroids do not occur until four to six hours after the start of therapy and may only become apparent after one or two weeks of continuous therapy.

The optimal initial dose of corticosteroid for the treatment of asthma has not been determined. Outpatients can often be effectively treated with the equivalent of 30 to 40 mg per day of prednisone. Some patients with severe prolonged exacerbations of asthma appear to require considerably higher initial doses. An initial dose of 60 mg of prednisone or an equivalent dose of methylprednisolone acetate every six hours is thus commonly recommended for patients who are sick enough to require admission to hospital for an exacerbation of asthma. Although corticosteroids are often administered intravenously to patients with status asthmaticus, prednisone is rapidly and completely absorbed from normal gastrointestinal tracts. In that the onset of corticosteroid action is slow (no appreciable effect on lung function occurs before four to six hours after administration), intravenous administration is often unnecessary. The optimal duration of corticosteroid therapy varies considerably among patients. Although some physicians prescribe a standardized rapidly tapering course of prednisone, this approach often results in early recurrence or inadequate initial improvement. It is preferable to continue the initially prescribed dose of corticosteroid until a clear-cut objective improvement in airway function has occurred. The rate at which to decrease subsequent steroid doses can then be individualized on the basis of the duration and severity of the patient's exacerbation and the patient's history of previous steroid requirements.

A recurrence of airway obstruction during or soon after a tapering course of corticosteroids usually indicates a requirement for long-term anti-inflammatory therapy. In many patients inhaled corticosteroids can eliminate or at least diminish long-term requirements for systemic corticosteroids. Because inhaled steroids are poorly tolerated during acute exacerbations of asthma, treatment with these drugs should be initiated when a patient's asthma is in remission (usually during a course of systemic corticosteroids). As with β-adrenergic agonists, inhaled corticosteroids have dose-dependent beneficial effects at doses well above those commonly recommended by their manufacturers. Thus, 24 inhalations per day (1,008 μg) of beclomethasone dipropionate are commonly effective in weaning patients from systemic corticosteroids who could not be weaned on a standard dose of eight inhalations per day. The increased incidence of oral candidiasis that results from the use of high doses of inhaled corticosteroids can be notably diminished if these drugs are inhaled through one of a number of commercially available spacers that diminish oropharyngeal deposition of the aerosol delivered from a metered-dose inhaler. The incidence of oral candidiasis may also be diminished if patients routinely wash their mouths with water after inhaling the drug. Because inhaled corticosteroids may cause bronchospasm, they are frequently administered after inhalation of a β-adrenergic agonist.

In patients who cannot be weaned from systemic corticosteroids despite the use of inhaled corticosteroids, inhaled cromolyn is occasionally effective. Alternate-day administration of corticosteroids has been shown to reduce the incidence of many of the complications of systemic steroid therapy. Because of the episodic nature of asthma, however, a stable alternate-day regimen is often difficult to achieve.

Despite the available methods for weaning patients from systemic corticosteroids, some patients with asthma continue to require long-term treatment with these drugs. The serious side effects that result underscore the inadequacy of the present approach to anti-inflammatory therapy in asthma and the urgency of developing more specific pharmacologic agents.

Mucus Hypersecretion

Although mucus hypersecretion is widely believed to contribute significantly to airway obstruction in status asthmaticus, none of our present therapies has been shown to treat this abnormality. Recent studies suggest that the most commonly used class of bronchodilators, β-adrenergic agonists, increases protein secretion from submucosal glands and thus increases the viscosity of mucus. This effect would not be expected to be beneficial. New information about the control of mucus and water secretion in the airways has suggested several possible pharmacologic approaches to mucus hypersecretion, but none has yet been studied in patients with asthma. Although hydration, airway humidification and chest physiotherapy have all been advocated to treat the consequences of mucus hypersecretion, these approaches have little scientific basis. None has been shown to produce clinical benefit in patients with asthma. The development of effective methods to treat mucus hypersecretion in asthma should thus be a major focus of future clinical research.

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